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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/284,233	07/28/99	MEYER	T P564-9008

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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1645	10

DATE MAILED: 07/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/284,233	Meyer et al
Examiner	**Group Art Unit**
Portner	1641

X Responsive to communication(s) filed on *Jul 28, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-16* is/are pending in the application.

Of the above, claim(s) *16* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *1-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

X Claims *1-16* are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

X Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

X All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

X received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *1*

☐ Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Claims 1-16 are pending, claims 1-15 are under consideration.

Election/Restriction

1. Claim 16 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected Group II. Election was made **without** traverse in Paper No. 9, dated April 21, 2000.

Sequence Letter

2. The sequence disk submitted in response to the previously sent SEQUENCE Letter is in compliance. The examiner noted the presence of sequences that are in the case that have not been assigned a SEQ ID NO.

a. Sequences contained within the submitted figures must be referred to by SEQ ID No in the Brief Description of the drawings or in the figures. Please see Figure 2.

b. Oligonucleotides on page 13 of the instant specification need SEQ ID No assigned or inserted next to the sequences of 9 or more nucleotides.

Information Disclosure Statement

3. The information disclosure statements filed June 8, 1999 and July 29, 1999 have been considered as to the merits prior to first action.

Drawings

4. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. Please insert the following heading prior to the brief description of the figures on page 10, line 12. Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

Priority

7. If applicant desires priority under 35 U.S.C. 119 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now patent no." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

8. The first sentence of the specification does not refer to the priority documents upon which Application is based; amendment of the specification to reflect the foreign priority entitled to this Application is requested, specifically PCT/EP97/04744.

9. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. PCT/EP/04744, filed on September 1, 1997.

Claim Rejections - 35 U.S.C. § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 6, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 recites on line 5 the phrase "said pathogen". The phrase lacks antecedent basis in the claim. It is not clear that the "attenuated bacterium" and "said pathogen" are one in the same bacterium. An attenuated bacterium may cause no infection at all and therefore would not be a pathogen. The recitation of language that appears to define materially different compositions to be contained within the same composition is confusing.

b. Claim 1(and all claims dependent therefrom) recites the phrase "said nucleic acid molecule in a target cell." It is not clear how the nucleic acid molecule would be expressed in a

target cell, if the nucleic acid sequence were not incorporated into the cell in some way. What the target cell that would express the heterologous nucleic acid molecule is not distinctly claimed. The claim appears to be reciting limitations directed to the transformation of a target cell for the expression of the heterologous nucleic acid. But this process step is not distinctly claimed. Clarification of what this phrase means is requested.

c. Claim 1 recites a composition the only contains a single component and therefore does not distinctly claim a pharmceutical composition. Pharmaceutical compositions are often understood to be mixtures of at least two components. Amendment of the claim to recite -- a pharmaceutical carrier-- could obviate this rejection.

d.Claim 13 recites the phase "a pharmaceutically effective amount". This amount needs to be effective, but the effectiveness is not defined to be effective for inducing a protective immune response. The method does not recite a step of providing the antigen and therefore recites an incomplete method. This rejection could be obviated by amending the claim to recite --providing the antigen of claim 1-- followed by the step of formulating now recited. Therefore Applicant's invention is not distinctly claimed.

e. Claim 6 recites abbreviations. Abbreviations should be clearly define upon their first appearance in the claims.

f. Claim 12, recites two different modes of administration which do not further limit claim 1, from which it depends. How the structural components are modified based upon the mode of administration is not distinctly claimed.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of recombinant DNA, vectors, host

cells, chimeric proteins and antigenic compositions that comprise Helicobacter antigens the instant specification, does not reasonably provide enablement for preventive or therapeutic live vaccines that express any Helicobacter antigen, and compositions which comprise any nucleic acid sequence from Helicobacter as the active agent which is a mimotope or any antigen that is encoded by a nucleic acid sequence that does not evidence original descriptive support. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

14. The claims recite a pharmaceutical composition that comprises a live vaccine that comprises a Helicobacter heterologous nucleic acid molecule encoding a Helicobacter antigen or mimotope. Mimotopes may be confirmational epitopes that correspond to a specific receptor or may be represented by linear epitope amino acid sequences. The specification teaches compositions comprising urease, a known protective antigen and their administration for induction of a protective immune response, as well as the use of nucleic acid sequences from AlpA or AlpB.

The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity, in the case of the instantly claimed invention, the protection or prevention of infection would be

against pathogenic *Helicobacter*. No specific amounts of antigen are recited in the claims. No specific protective mimotopes, synthetic peptides that mimic antigen epitopes, are disclosed. A representative number of protective mimotope species has not been provided to enable the claimed genus of protective mimotopes for use in vaccine formulations. Data obtained from experiments must demonstrate an art recognized standard of improvement over the control in order for the composition to be considered as being useful for treatment or prevention of infection, especially treatment and prevention of Helicobacter infection. This information is essential for the skilled artisan to be able to use the claimed composition (vaccines) for their intended purpose. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced which would prevent or treat gastric cancer. It is also not clear that any expressed mimotope, with a molecular weight of less than 1000 Daltons would be recognized as an immunogen. Mimotopes may be as small as 3-5 amino acids and therefore would not evidence a molecular weight high enough to stimulate an immune response, no less a protective immune response, which is necessary to define the composition as a vaccine.

The prior art teaches that Helicobacter pylori vaccines are unpredictable, specifically, in the type of effect they will have on preventing or treating infection; the ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity is problematic. In HP WORLD-WIDE, a publication from Brocades Pharma BV Leiderdorp, The Netherlands, February 1992, data was presented stating that immunization does not appear promising. Parenteral immunization of specific pathogen free mice with *H. felis* gave no protection against gastric colonization; previous oral infection only delayed colonization (Heap,K, Australia). The article also taught that "although intra-peyers patch immunization of killed *H. pylori* in rats shows that the gut mucosa can mount a vigorous immune response, oral immunization with either live or killed bacteria induced no significant serum or salival antibody response (Dunkley, M, Australia). Blaser also warned that because of the possible autoimmune component of the disease the wrong vaccine could actually make things worse." Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

Given the lack of guidance on how to obtain the desired effect using any composition comprising any active ingredient for the prevention or therapeutic vaccine in a method of treating any disease caused by Helicobacter in light of the teachings of the prior art which teaches that vaccines comprising Helicobacter antigens are unpredictable in methods of treating or preventing infection the skilled artisan could not make and use the claimed invention. No evidence is of record showing that **any** composition could confer the desired and claimed effect. No working examples are shown which convey the missing information or show the nucleic acid sequences that upon expression as a heterologous antigen in an attenuated bacterium would serve to induce a protective immune response against Helicobacter infection and disease. Therefore, the skilled artisan could not use **any** recombinant bacterium that comprises a heterologous nucleic acid that would express the encoded Helicobacter antigen, or mimotope of said antigen, to obtain the desired effect of preventing or treating infection without undue experimentation.

Claim Rejections - 35 U.S.C. § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Please Note: The following rejection are being made in light of the claimed compositions being read as recombinant attenuated bacterium cells that have been transformed to express a heterologous Helicobacter antigen.

16. Claims 1,2,5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al (1993).

Evans et al (1993) shows the cloning, nucleotide sequence and expression of a nucleic acid sequence encoding an adhesin subunit of Helicobacter pylori in an attenuated enterobacterial cell, wherein the cell was an E.coli K-12 strain DH5alpha (see page 674, col. 2, Materials and Methods, first paragraph) and HB101. The recombinant attenuated bacterium comprised at least one heterologous nucleic acid molecule from Helicobacter pylori adhesin (claim 1-2, instant invention). An adhesin would be a protein secreted to the surface of Helicobacter for the purpose of interacting with host cell receptors (claim 5, instant invention).

The recombinant attenuated bacterium does comprise at least one second nucleic acid molecule that is immunomodulatory, wherein the claimed invention does not require that the second nucleic acid be a heterologous nucleic acid sequence and therefore reads on an expressed immunogenic antigen of the recombinant bacterium. E.coli comprises many immunomodulatory antigens that are expressed and therefore meets the required limitations of claim 10 of the instant invention as now claimed.

The expressed Helicobacter antigen was immunostimulatory, immunoreactive and used to detect the adhesin binding sequences for host epithelial cells. An immune response obtained from immunization with the adhesin receptor sequence synthesized peptide blocked hemagglutination of human erythrocytes by H.pylori (page 682, col. 2, paragraph 2). Therefore, the reference discloses and anticipates the now claimed composition that comprises a recombinant attenuated bacterium that comprises at least one Helicobacter antigen.

17. Claims 1-2, 5-6,7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Odenbreit et al (April 1996).

Odenbreit et al disclose the use of insertional mutagenesis for the production of attenuated microbial strains of Helicobacter pylori, as well as transformed strains of E.coli that were produced through the use of a novel TnMax9 mini-blaM transposon to establish a Helicobacter gene library in E.coli . The cloned polynucleotides were used in the natural transformation (see page 364, col. 1) of H.pylori strains to produce 135 distinct Helicobacter

pylori mutant strains (reference summary, page 361), wherein two strains evidenced significantly reduced adherence to KatoIII cells (see Table 1, strains P1-140 and P1-179a). The reference discusses these strains with respect to the relative adherence activity to wild type Helicobacter and concludes that the two mutant strains evidenced insertional mutagenesis in the same locus but at different positions. Strain P1-140 showed an interrupted ORF that started 69 nucleotides upstream of the insertion site and continued to the end of the obtained sequence. The putative protein N-terminal sequence was determined and corresponded to a gene for an exported protein. (see page 366, col. 2, paragraph 2 and page 367 both columns at bottom of page). The transformed strain P1-140 expressed the adhesin protein but at a very reduced level, approximately 10% of that of wild-type strains. The open reading frames were determined to correspond to nucleic acid sequences that encode adherence proteins as shown through the disruption of bacterial binding to the corresponding receptors on eukaryotic cells. (See page 369, col. 2). The disclosed mutant strain of E.coli that encoded the heterologous nucleic acid sequence (plasmid used to produce clone P1-140)would be capable of causing the expression of the nucleic acid molecule in a target cell anticipates the now claimed invention. The target cell could also be the production of an attenuated Helicobacter pylori strain (P1-140) produced through the natural transformation of Helicobacter pylori with the transformed E.coli. The clones that comprised the plasmids were referred to as pMu140 and pMu179a (see page 367, bottom of page col. 1). The disclosed strain P1-140 anticipates the now claimed invention of 1-2, 5-6,7-10 as the attenuated microbial pathogen is a Helicobacter pylori stain

that encodes a heterologous nucleic acid sequence that corresponds to and encodes an adhesin protein of Helicobacter pylori which was produced through natural transformation using an attenuated E.coli strain that comprised the heterologous nucleic acid sequence. The encoded protein is not referred to as AlpA or AlpB but the disclosure of the reference teaches that the mutant strains comprised heterologous DNA that encoded a protein not previously known and directly corresponded to the cells ability or inability to adhere to KatoIII epithelial cells and therefore defines a protein adhesin of Helicobacter pylori. If applicants contend that this is not the case, applicants are advised that the Office does not have the facilities for examining and comparing applicant's product with the prior art, and that the burden is on applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. and Int.).

18. Claims 1-2, 5, 10, 11,12,13 are rejected under 35 U.S.C. 102(b) as being anticipated by Doidge (WO95/33482) in light of McKee (1992).

Doidge et al teach recombinant expression vectors for Helicobacter pylori catalase. The production of attenuated E.coli and Salmonella expression vector host cells are taught, in light of Mckee, (see Doidge page 5, lines 4-18; and page 8, lines 8-27), which comprise Helicobacter nucleic acids, and vaccines which comprise expressed proteins. (Mckee

was incorporated by reference and teaches the use of attenuated recombinant Salmonella strains (page 84, col. 2, Selective delivery section) . Doidge et al claim preparations that are pharmaceutical compositions that comprise a recombinant bacterium that express a heterologous Helicobacter nucleic acid molecule and teach methods of using the compositions for the prevention of infection using a recombinantly expressed catalase antigen. The reference inherently discloses the now claimed invention.

19. Claims 1,2,4,5, 10, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Dore'-Davin et al (May 1996).

Dore'-Davin et al utilize a laboratory strain of E.coli in the production of a recombinant bacterium, wherein the bacterium is an enterobacterial cell and comprises a heterologous nucleic acid that encodes a protective Helicobacter pylori urease fragment. The antigen was expressed by the recombinant bacterium and was purified. Inherently the disclosed recombinant E.coli that comprises a heterologous Helicobacter antigen anticipates the now claimed invention.

20. Claims 1-2,4-5,10-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Michetti (WO95/22987).

Michetti et al teach the formulation of genetically engineered attenuated live vectors that comprise bacterium (see page 23, lines 11-12), wherein the bacterium is taught to

be Salmonella typhimurium, Salmonella typhi, Shigella, Bacillus, Lactobacillus, BCG, E.coli, Vibrio cholerae or Campylobacter.(see pages 35-36, line bridging these pages). The compositions would comprise a carrier liquid such as saline or sodium bi-carbonate(page 23, lines 22-25) and enteric coated capsules or microspheres. The mode of administration is by oral, nasal, rectal or ocular routes and take the form of an aerosol, suspension, capsule or suppository (page 25, lines 5-15). E.coli was used to produce recombinant Helicobacter pylori urease subunits (see page 53, lines 5-6) . Inherently the reference discloses the now claimed invention (see Michetti, claims 25-26 and 61-62).

Claim Rejections - 35 U.S.C. § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-3,4-5,6-9,10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michetti (WO95/22987) in view of Russell et al (US Pat. 6,030,624) .Claims 1-2,4-5,10-15 are rejected under 35 U.S.C. 102(b) as being anticipated by

See discussion of Michetti above. Michetti et al teach the formulation of genetically engineered attenuated live vectors that comprise bacterium (see page 23, lines 11-12), wherein the bacterium is taught to be Salmonella typhimurium, Salmonella typhi, Shigella, Bacillus, Lactobacillus, BCG, E.coli, Vibrio cholerae or Campylobacter.(see pages 35-36, line bridging these pages) but differs from the instantly claimed invention by failing to show the use of an AroA mutant strain..

Russell et al show the formulation of genetically engineered attenuated live oral or intranasal S.typhimurium delta-AroA, delta-AroD mutant vectors under the control of bacteriophage T7 transcription (col. 3, lines 55-63 and claims) for the expression of heterologous DNA from Helicobacter pylori (col. 9, lines 28-30, lines 35-37, lines 39-45 and lines 66) linked to Vibrio cholera toxin A2/B subunits nucleic acid sequences in an analogous art for the purpose of recombinantly producing and expressing chimeric proteins for stimulating a mucosal immune response (abstract, figures, col. 3, lines 37-46; col. 1, lines 45-67 and col. 2, lines 1-3) against pathogens, to include Helicobacter and Salmonella.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the invention of Michetti in view of the teachings of Russell because Russell show the formulation of live oral vaccines that comprise attenuated AroA live Salmonella host cell vectors for the induction of a mucosal immune response to heterologous DNA, wherein the use of the live attenuated AroA mutant strain provides means for antigen presentation directly to mucosal inductive surfaces and obviates the need for

antigen purification (col. 3, lines 50-55) and Russell et al clearly teaches that advantage of utilizing non-toxic chimeric proteins which comprise CTA2/B fusion proteins for the induction of IgA antibodies to protect mucosal surfaces of the gastrointestinal tract, and the use of attenuated recombinant host cells which express a heterologous antigen overcomes the problems associated with oral immunization of protein immunogens which become denatured by gastric acid and digestive enzymes, limited adsorption by the intestinal mucosa and clearance by peristalsis, wherein a recombinant host cell which is avirulent would function as a live vaccine delivery system with tropism for the gut associated lymphoid tissue and Helicobacter is a known mucosal pathogen which induces chronic infection leading to gastritis and gastric ulcers. The combination of the two references teach recombinant host cells for the expression of Helicobacter antigen linked to a second heterologous nucleic acid that encodes an immunogenic cholera toxin A2/B subunit. Michetti clearly teaches the use of attenuated strains of bacteria for the expression of heterologous Helicobacter DNA and claims the use of recombinant Salmonella and Russell provides motivation to the person of ordinary skill in the art by teaching means, methods and modes of administration of expecting reasonable success in stimulating a mucosal immune response against Helicobacter. In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a chimeric recombinant Helicobacter antigen-A2/B cholera toxin fusion protein because Russell suggests the production of a Helicobacter antigen/A2-B cholera chimeric protein and recombinant DNA, as well as teaches means,

methods, expression vectors, host cells and multiple advantages of utilizing a chimeric protein and a recombinant host cell which expresses the chimeric protein for inducing a mucosal immune response which would be provide for reducing or preventing infection caused by Helicobacter.

23. Claims 1-4,7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al (US Pat. 6,030,624) in view of Bukanov et al (1994).

Russell et al disclose the formulation of recombinant DNA which comprises the ligation of Vibrio cholera toxin A2/B subunits nucleic acid sequences with a heterologous polynucleic acid sequence and teach the incorporation of the recombinant DNA into an expression vectors and host cells (E.coli and S.typhimurium), teaches a process for the production of the chimeric protein from the recombinant host cell, as well as a method of inducing a mucosal immune response (abstract, figures, col. 3, lines 37-46; col. 1, lines 45-67 and col. 2, lines 1-3; . The reference suggests the formulation of recombinant DNA, expression vectors, host cells, chimeric proteins and a method of producing a chimeric protein which comprises Helicobacter pylori (col. 9, lines 28-30, lines 35-37, lines 39-45 and lines 66) DNA but differs from the instantly claimed invention by failing to show specific sequences for Helicobacter.

Bukanov et al teach Helicobacter nucleic acids and E.coli expression vector host cells which comprise Helicobacter nucleic acids in an analogous art for the purpose showing

Helicobacter genes for known antigens associated with disease, specifically Helicobacter cytotoxin (VacA), cytotoxin associated protein (CagA), urease and regulatory functions (ureAB, ureD, and ureH), catalase (katA), major and minor flagellin(flaA and flaB), heat shock (stress) and chaperone proteins, an adhesin subunit (hpaA, flagullar sheath protein analogous to Fliq) and a surface protein of 26 kDa (see page 509, summary; page 516, Table 2; Figure 9, col. 1; and entire document).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the invention of Russell in view of the teachings of Bukanov because Bukanov teaches specific Helicobacter nucleic acid sequences which encode Helicobacter UreB antigen, as well as other antigens associated with disease and Russell clearly teaches the advantage of utilizing non-toxic chimeric proteins which comprise CTA2/B fusion proteins for the induction of IgA antibodies to protect mucosal surfaces of the gastrointestinal tract by blocking microbial adherence and colonization, and the use of attenuated recombinant host cells which express a heterologous antigen overcomes the problems associated with oral immunization of protein immunogens which become denatured by gastric acid and digestive enzymes, limited adsorption by the intestinal mucosa and clearance by peristalsis, wherein a recombinant host cell which is avirulent would function as a live vaccine delivery system with tropism for the gut associated lymphoid tissue and Russell teaches the use of Helicobacter nucleic acids for the advantages set forth above, because Helicobacter is a known mucosal pathogen which induces chronic infection leading to gastritis

and gastric ulcers. In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a chimeric recombinant Helicobacter UreB-antigen-A2/B cholera toxin fusion protein because Russell suggests the production of a Helicobacter antigen/A2-B cholera chimeric protein and recombinant DNA, as well as teaches mean, methods, expression vectors, host cells and multiple advantages of utilizing a chimeric protein and a recombinant host cell which expresses the chimeric protein for inducing a mucosal immune response which would be provide means of reducing or preventing infection caused by Helicobacter and Bukanov teaches that various Helicobacter antigens, to include UreB and CagA, antigens which have been shown to be associated with gastric infection and would therefore be functional a equivalent of the now claimed invention.

Conclusion

24. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

25. Blaser (US Pat. 5,527,678), Labigne et al (US Pat. 5,843,460; WO94/26901), Hu et al (1993),Bergonzelli et al (April 1996), Corthesy-Theulaz et al (1995), Clancy et al (1996), Newell (1994), Ferrero et al (1993), Kolesnikow et al (1996), Lindberg (1995), Tummuru et al (1993), Leying (1992) and Cover et al (WO94/09023), Pesci et al (1994). are being made of record and not applied in an art rejection under 35 U.S.C.

103 as the references are cumulative but would be applied if the claims were amended in such a way as would necessitate their application to the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
July 6, 2000

ANITA MINNIFIELD
PRIMARY EXAMINER